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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,822	04/24/2001	Thorvald Eelco Wallaart	702-010272	3747

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EXAMINER	
SAIDHA, TEKCHAND	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,822	WALLAART ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43,45-65 and 75-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *43,45,47-65 and 75-86* is/are rejected.

7)☐ Claim(s) *46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

NON-FINAL

1. Applicants' Amendment filed September 29, 2004 is acknowledged. Applicant's arguments filed September 29, 2004 have been considered and not found to be persuasive. The reasons are discussed following the rejection(s).

2. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

3. **Claims withdrawn** :

Claims 66-74 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed. Claim 44 has been canceled.

4. Claims 43, 45-65 and 75-86 are under consideration in this examination.

5. **Rejoinder** (Clarification): Applicants misinterpret Examiner's position by stating that method claims 69 & 71-74 which recite the DNA of SEQ ID NO: 13, will be re-joined as a matter of right.... This is incorrect because claims 72-74 are drawn to a 'source of artemisinin', which is not a method claim, and will not be included in any rejoinder to the currently prosecuted DNA claims (or product claims). Further, to help Applicants in the prosecution of claims 72-74, any 'artemisinin' compound sold by any chemical company will read on the product 'artemisinin'. A company making the compound may be considered a 'source'. Further, these claims as present have other issue that need to be resolved.

6. ***35 U.S.C.§ 112, first paragraph (Written Description)***

Claims 64-65 & 75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 64-65 & 75 are drawn to transgenic cell, tissue or organism comprising a transgenic tissue or transgenic organism consisting at least a part of host cells containing an isolated DNA sequence encoding a polypeptide having the enzymatic activity of amorpha-4,11-diene synthase, wherein the DNA sequence exhibits at least 70%homology to SEQ ID NO: 13; or wherein, the DNA sequence is obtained from a plant and wherein the DNA construct is used for preparation of a vector, host cell, transgenic cell, tissue or organism.

The specification, however, only provides the expression of a single plant DNA [from *Artemisia annua* (sweet wormwood)] construct of SEQ ID NO: 13 in *Escherichia coli*. There is no description of either expression of parts of host cells (claims 64 & 65) and/or details of obtaining transformed tissue or organism which may be a human tissue or human. Without such a description, extending the teachings of a single species expression construct of SEQ ID NO: 13 in *Escherichia coli* to a genus of expressing such a DNA into any tissue or organism, is lacking written description for the genus.

Given this lack of additional representative species, pertaining to the expression into any tissue or organism of the DNA which is 70% similar to SEQ ID NO: 13 or any tissue or organism containing a part of the host cell (claims 64 & 65) and the associated

activity [amorpha-4,11-diene synthase] encoded by these innumerable DNA molecules, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Therefore, the written description requirement is not satisfied.

Applicants' Arguments:

Applicants argue that claim 43 has been amended to recite 'that the isolated DNA exhibits 70% homology to SEQ ID NO: 13', and therefore the specification provides adequate written description.

In response, and as per the written description guidelines 'claim reciting structure and function' do not lack written description, as related to the DNA sequence. However, the claims drawn to transgenic tissue or organism, still lack adequate written description for the reasons explained above, and therefore, the rejection is maintained only for claims 64-65 & 75.

7. ***35 U.S.C.§ 112, first paragraph (Enablement)***

Claims 43, 45, 47-65 and 75-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated DNA sequence of SEQ ID NO: 13 encoding an amorpha-4,11-diene synthase of SEQ ID NO: 14, does not reasonably provide enablement for a DNA sequence that is 70%, 80%, 90% or 95% (claims 43, 45 & 85-86) identical to SEQ ID NO : 13 and encodes a protein having

amorpha-4,11-diene synthase activity or any host tissue or organism transformed with such a DNA.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988))[*Ex parte* Forman [230 USPQ 546 (Bd. Pat. App. & Int. 1986)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim. The factors most relevant to this rejection are [the scope of the claims, unpredictability in the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

The specification provides guidance and examples for making an isolated DNA sequence comprising SEQ ID NO: 13 and the encoded polypeptide sequence of SEQ ID NO: 14 [amorpha-4,11-diene synthase]. However, the specification does not teach the specific structural/catalytic amino acids and the structural motifs essential for protein activity/function which cannot be altered. The state of the art as exemplified by Attwood et al. [Comput. Chem. 2001, col. 54(4), pp. 329-39] is such that "..we do not fully understand the rules of protein folding, so we cannot predict protein structure;

and we cannot invariably diagnose protein function, given the knowledge only of its sequence or structure in isolation" (see abstract and the entire publication). Further Ponting [Brief. Bioinform. March 2001, Vol. 2(1), pp. 19-29] states that "...predicting function by homology is a qualitative, rather than quantitative process and requires particular care to be taken, due attention should be paid to all available clues to function, including orthologue identification, conservation of particular residue types, and the co-occurrence of domain in proteins" (see abstract and the entire publication).

The standard of meeting enablement requirement is whether one of skill in the art can make the invention without undue experimentation. The amount of experimentation to make the claimed polynucleotide is enormous and entails selecting specific nucleotides to change (deletion, insertion, substitution or combination thereof) in a polynucleotide to make a claimed polynucleotide and determining by assays whether the polypeptide has activity. The specification does not provide guidance with respect to the specific structural/catalytic amino acids and the structural motifs essential for enzyme structure/function which must be preserved. Thus, searching for the specific nucleotides to change (deletion, insertion, substitution or combination thereof) in a polynucleotide to make polynucleotide that is at least 70%, 80%, 90% or 95% identical to a polynucleotide comprising nucleotide sequence of SEQ ID NO: 13 is well outside the realm of routine experimentation and predictability in the art of success in determining whether the resulting polypeptide has activity (same, other or none) is extremely low since no structural motifs essential for enzyme structure and

activity/function which must be preserved. Similarly transforming any tissue or organism which may be human tissue or a human is neither exemplified nor enabled. Claims drawn to transgenic tissue or organism (claims 64-65) containing at least a part of host cell consisting of SEQ ID NO: 13 is also not enabled for the foregoing reasons.

Applicants' attention is specially drawn to Accession No. AF327526 [Liu et al, 2001, not prior art], a DNA sequence encoding sesquiterpene cyclase [CN : Farnesyl pyrophosphate cyclase] and is 98.6% identical to Applicants' SEQ ID NO: 13. [see the enclosed sequence search alignment]. As can be seen, a difference of 0.4% between Accession No. AF327526 and Applicants' SEQ ID NO: 13, results in the DNA encoding a totally different protein having different enzyme activity. Therefore, modifying a DNA sequence encoding amorpha-4,11-diene synthase by 5-30% will be highly unpredictable, and based upon the works of Liu et al., most likely will not produce a DNA capable of encoding a protein having amorpha-4,11-diene synthase activity.

Further, the specification does not support the broad scope of the claims which further encompass transgenic tissues or microorganisms comprising such DNA sequences encoding amorpha-4,11-diene synthase from any source or expression of parts of host cells (claims 64 & 65) and/or transformed tissue or organism which may be a human tissue or human, because the specification only teaches a single DNA species capable of encoding amorpha-4,11-diene synthase from *Artimisia*. The prior art is silent about DNA from other plants, microorganisms, etc., which are capable of encoding amorpha-4,11-diene synthase.

Therefore, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific catalytic amino acids and structural motifs essential for activity/function which must be preserved and/or other DNA sequences encoding amorpha-4,11-diene synthase, apart from disclosure to transforming any tissue to organism including a human or a human tissue in order to enable a skilled artisan by providing guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification) and which of the human tissue or human are capable of being transformed by a plant gene, and detailed knowledge of the ways in which the proteins' structure relates to its function. Without such a guidance, the experimentation left to those skilled in the art is undue.

Applicants' Arguments:

Applicants argue that there is sufficient guidance in the specification, example 2-3, teaching isolation and characterization of the gene encoding amorpha-4,11-diene synthase, total isolation of RNA, the synthesis of cDNA and the construction of cDNA library and farnesyl pyrophosphate (FPP) assay. Applicants submit that the FPP assay described in the examples more than adequately enables one skilled in the art to isolate DNA sequence that are 70% homologous to SEQ ID NO: 13 without undue experimentation and without the need for further teachings related to specific structural motifs necessary for unaltered protein activity/function.

Applicants' arguments have been considered and found not relevant because the points raised by the Applicants do not teach or enable a skilled artisan to modify a protein by 30%.

Further, Applicants have not responded to arguments pertaining to Accession No. AF327526 [Liu et al, 2001, not prior art], wherein a DNA sequence encoding sesquiterpene cyclase [CN : Farnesyl pyrophosphate cyclase] was found to be 98.6% identical to Applicants' SEQ ID NO: 13. [sequence search alignment, previously provided]. Therefore, a 0.4% change in the sequence identity resulted in the DNA encoding a functionally distinct protein. The rejection is therefore maintained.

8. Claims 85-86 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 85-86 depend upon canceled claim 44. Placing the claims in proper dependent form, for example, will overcome this objection.

9. Claim 46 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. Status of the claims:
Claims 43, 45-65 and 75-86 are pending.
Claim 46 is objected.
Claims 43, 45, 47-65 and 75-86 are rejected.

11. Claims drawn to Specific SEQ ID NO:, without the homology language, free of language such as 'transgenic tissue or organism', will be in a better condition for allowance. Substituting 'transgenic tissue or organism' with 'transgenic plant tissue or transgenic plant' is suggested as an alternate language

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272 0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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November 23, 2004